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EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/801,956	FUJIMOTO ET AL.	
	Examiner	Art Unit	
	Steven C. Pohnert	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12,13,17-21,26-30,35-39,44-49,52,53,58-63,71-74 and 81-96* is/are pending in the application.

4a) Of the above claim(s) *4,9,20,29,38,48,62 and 71-73* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10,12,13,17-20,26-28,30,35-39,52,53,58-61,63 and 81-96* is/are rejected.

7)☒ Claim(s) *1-5* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 June 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed 2/28/2007. Currently claims 1-10, 12-13, 17-21, 26-30,35-39, 44-49, 52-53, 58-63, 71-74, 81-96 are pending. Claims 9, 20,29, 38, 48, 71-73 have been withdrawn from consideration. Claim 4 is drawn in part to D12S1657, D12S393, D12S1706, and D12S346 markers, while this claim has been withdrawn by applicant it does encompass the elected invention. The generic claim are examined as directed to the elected combination of all 4 recited markers. It is noted that applicant elected the combination of D12S1657, D12S393, D12S1706, and D12S346 markers.

The arguments as to the priority are convincing and the applicant is entitled to priority date of provisional document.

The objections to the claims have been overcome by amendment.

This action contains new grounds of rejection necessitated by amendment.

An action on the merits of claims 1-8, 10, 12, 13, 17-20, 26-28, 30, 35-39, 52, 53, 58-61, 63, and 81-96 follows.

Maintained Rejections

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-8, 10-19, 21-28, 30-37, 39-47, 49-61, 63-70, and 74-80, 93-96 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting melanoma in a human subject comprising detecting the combination of D12S1657, D12S393, D12S1706, and D12S346 markers in the 12q22-23 region in plasma or serum samples wherein the presence of the combination is indicative of incidence and progression of melanoma occurrence, does not reasonably provide enablement for detecting one or more DNA Markers in the 12q22-23 region extending from D12S1657 to D12S346. The specification is not enabling for the correlation of the 12q22-23 region to specifically colon, brain, or breast cancer. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors have been described by the court in re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in the Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claims are broadly drawn to methods of detecting one or more DNA marker in the 12q22-23 extending from D12S1657 to D12S346 in a human subject. The claims are further drawn to the LOH of "any" 12q22-23 marker or "any" combination of 12q22-23 markers in human subject and "any" subject with cancer. The claims are further drawn to detecting melanoma, colon cancer, brain cancer and breast cancer. Further the claims are drawn to the detection of melanoma in a patient wherein the in the loss of D12S1657, D12S393, D12S1706, and D12S346 is indicative of melanoma. The claims are further drawn to the staging or progression of melanoma or colon cancer based on the presence of the D12S1657, D12S393, D12S1706, and D12S346. The claims are further drawn to determining the probability of survival of a subject suffering from stage III or stage IV melanoma. The claims are further drawn to determining the probability of responsiveness to melanoma biochemotherapy. Claim 93 is further drawn to the detection of colon or breast cancer by LOH of any of D12S1657, D12S393, D12S1706, and D12S346.

The amount of direction or guidance and the Presence and absence of working examples in the specification.

The specification teaches there is an unexpected LOH of markers for 12q22-23 (see page 3, lines 5-8). The specification further teaches that the 12q22-23 region encompasses the APAF-1 locus (see page 9, line 26) and there was a statistically significant allelic imbalance in metastatic tumors and primary melanoma (p=0.02)(see page 9, lines 28-29). Further APAF-1 loss was significantly correlated with a worse

prognosis ($p<0.05$) (see page 10, 1st line). The specification further teaches melanoma patients that responded to chemotherapy had a significantly lower frequency of allelic imbalance at 12q22-23 ($P<0.029$) and better prognosis ($p<0.046$) (see page 10 line 12-13), then patients with an allelic imbalance. Further the specification teaches the use of 12q22-23 markers: D12S1657, D12S393, D12S1706, and D12S346.

The specification teaches LOH frequencies in primary melanomas were 20%, 31%, 13% and 17% at D12S1657, D12S393, D12S1706, and D12S346, respectively (see table 1). The specification teaches LOH frequencies in metastatic melanomas were 23%, 35%, 17% and 21% at D12S1657, D12S393, D12S1706, and D12S346, respectively (see table 1). The specification asserts that there is a higher frequency of allelic imbalance in metastatic melanoma than primary melanoma ($P=0.02$), although there is no frequency differences between stage III melanoma and stage IV melanoma (see page 24,line 11 to page 15 line 1). The specification further teaches there is no correlation between APAF-1 status and overall survival in primary melanoma, but there is a statistically significant correlation between APAF-1 status and Stage III/IV melanoma ($p=0.05$) (see page 26, lines 10-15). Further survival of stage III metastatic melanoma and stage III metastatic melanoma with RLM was statistically correlated with APAF-1 status ($P=0.03$, $p=0.02$) but metastatic melanoma with ILM was not ($p=0.17$) (see page 26 line 25-page 26 line 3). It thus appears that LOH of D12S1657, D12S393, D12S1706, and D12S346 is correlated with survival of patients with stage III metastatic melanoma with RLM, but not survival with stage III metastatic melanoma with ILM. The

specification is silent on LOH of D12S1657, D12S393, D12S1706, and D12S346 and stage IV melanoma.

Further the specification teaches the effect of allelic 12q22-23 in serum samples on melanoma patient outcomes. The specification teaches a significant relationship of D12S1657, D12S393, D12S1706, and D12S346 markers ($p=0.029$) before chemotherapy in the responder group, but not in the responder group after chemotherapy (see page 36, line 11-15). It thus appears that chemotherapy results in LOH for D12S1657, D12S393, D12S1706, and D12S346 markers in melanoma. Further patients with D12S1657, D12S393, D12S1706, and D12S346 LOH had a statistically significantly worse survival rate ($p=0.046$) (see page 36, line 17) and response to chemotherapy was related to survival ($p<0.001$) (see page 36, line18).

The specification further teaches in tables 6, D12S1657, D12S393, D12S1706, and D12S346 LOH occur in no colon adenomas, 21% of primary colon cancers, or 54% of colon cancer derived liver metastases. Further the specification teaches in table 7, there are a D12S1657, D12S393, D12S1706, and D12S346 LOH in 25% of primary breast cancers. However the specification does not teach that the D12S1657, D12S393, D12S1706, and D12S346 LOH are statistically correlated with colon cancer or breast cancer. The specification does not teach any studies of D12S1657, D12S393, D12S1706, and D12S346 markers and brain cancer.

The specification does not teach any markers other then D12S1657, D12S393, D12S1706, and D12S346 to the 12q22-23 region or any other markers that are within the region. The specification does not teach a statistically significant relationship

between any cancer other then melanoma and 12q22-23 LOH. The specification does not even address brain cancer and 12q22-23 or teach a statistical relationship between LOH of D12S1657, D12S393, D12S1706, and D12S346 and breast or colon cancer. The specification does not teach that the markers for 12q22-23 are markers of APAF-1.

The specification does teach a statistically significant association of 12q22-23 LOH and melanoma, therapeutic response and outcome, but the specification teaches there is not a statistically significant relationship after chemotherapy, making the marker unpredictable for melanoma in those cases.

The specification does teach D12S1657, D12S393, D12S1706, and D12S346 are associated with melanoma and its progression and outcome. The specification teaches that the recited markers are associated with melanoma and response, before but not after chemotherapy. The specification further teaches the recited markers correlate with survival of type III melanoma with RLM, but not ILM. The specification teaches only D12S1657, D12S393, D12S1706, and D12S346 markers of 12q22-23. The specification does not teach a statistical relationship of recited markers with a cancer other then melanoma in subjects other than humans.

The state of prior art and the predictability or unpredictability of the art:

The prior art teaches that LOH 12q22-23 is common in metastatic melanoma (see abstract, Soegnas, et al Nature, 2001, vol 409, 207-211). The prior art teaches 12q22-23 LOH is indicative of poor response to chemotherapy, (see page 209, column 1, lines 8-10). The prior art does not teach a correlation between 12q22-23 LOH and any cancer other than melanoma.

The prior art does not teach 12q22-23 LOH is associated with "any" cancer other then melanoma. Soegnas teaches 12q22-23 marker, D12S327 (figure 1b), which the specification teaches does not teach but is encompassed by the claims. Further, Geneloc lists numerous other 12q22 markers that are encompassed by the claims, but are not taught in the specification. (see geneloc, bioinfo.weizmann.ac.il/cgi.bin/genloc/display_map.pl, pages 1-14).

The art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

The level of skill in the art:

The level of skill in the art is deemed to be high.

Quantity of experimentation necessary:

In order to practice the invention as claimed, one would first have to establish that a predicative relationship exists between LOH of 12q22-23 "any" markers extending from D12S1657 to D12S346 and melanoma, colon cancer, breast cancer or brain cancer. Experimentation would be replete with unpredictable trial and error analysis because the specification does not teach LOH of "any" 12q22-23 marker extending from D12S1657 to D12S346 is associated with melanoma, colon, brain or breast cancer, however the specification does teach melanoma is associated with the loss of D12S1657, D12S393, D12S1706, and D12S346. However, the specification teaches that the recited markers are lost following chemotherapy and are not predictive of survival in type III melanoma with ILM. As these markers are lost with chemotherapy and are not predictive of survival with type III melanoma with ILM they are not predictable markers for brain, colon or breast cancer in subject, or even "any" melanoma. The art confirms melanoma is associated with LOH of markers: D12S1657, D12S393, D12S1706, and D12S346, but one of skill in the art would have to recruit an enormous population of ethnically diverse subjects and brain, colon or breast cancer and cancer-free controls and determine the association of loss of "any" 12q22-23 marker extending from D12S1657 to D12S346 with melanoma, colon, brain, or breast cancer to determine a predictive relationship exists.

Due to the scope of the claims, one of skill in the art would be required to further undertake extensive trial and error experimentation to first determine a predictive relationship between loss of "any" 12q22-23 marker extending from D12S1657 to

D12S346 with melanoma, colon, brain, or breast cancer to determine a predictive relationship exists.

Therefore, in light of the breadth of the claims, the lack of guidance in the specification, the high level of unpredictability in the associated technology, the nature of the invention, the negative teachings in the art, and the quantity of unpredictable experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention as claimed.

Response to Arguments

The response filed on 2/28/2007 asserts on page 11 that newly amended claim 1 is fully enable by the specification. This argument has been fully considered and is not found persuasive because claim 1 is drawn to "any" marker between D12S1657 to D12S346. However as described above, the specification only has enables the detection of markers: D12S1657, D12S393, D12S1706, and D12S346. It is unpredictable which other markers in the D12S1657 to D12S346 are associated with melanoma, breast, colon or brain cancer.

The response filed on 2/28/2007 further asserts on page 12, that amended claim 6 is fully enabled by the specification. This has been fully considered but is not found persuasive because although the specification teaches that: D12S1657, D12S393, D12S1706, and D12S346 are lost in primary tumors and metastasis it does not teach that LOH of: D12S1657, D12S393, D12S1706, and D12S346 results in melanoma or any other cancer. Further the specification appears to teach that chemotherapy causes the LOH of: D12S1657, D12S393, D12S1706, and D12S346 in responders to

chemotherapy. Thus the patients that respond to chemotherapy treatment appear to be melanoma free and yet, would be considered to have melanoma according to the claim.

The response filed on 2/28/2007, also asserts on page 12, that claim 93 is fully enabled by the specification and directs attention to example 2, pages 31-40. The specification on pages 31-40 teaches an example in which there is a comparison of response of patients with melanoma (see page 31, line 13). It does not appear that a study of melanoma patients can adequately enable claims drawn to colon and breast cancer. It is noted that tables 6 and 7 appear to teach LOH of APAF-1 in patients with colon and breast cancer (see page 37). However, with respect to colon cancer it appears that of 103 patients with colon cancer only 4 demonstrated a LOH of APAF1. Further the specification teaches that no patients with colon adenomas (a type of colon cancer) had APAF-1 LOH. Further the claim 93 is drawn to the 12q22-23 region of chromosome 12, which is much larger than what appears to be taught by APAF-1 LOH in the specification. With respect to breast cancer the specification teaches 7 of 28% patients demonstrated an LOH of APAF-1. As mentioned previously this LOH is a much smaller region of chromosome 12 than the claims are drawn to. Further the examination of 28 patients is not a large enough sample to suggest the significance of this finding. Further it appears the teaching of tables 6 and 7 with respect to colon and breast cancer are biopsies of the tumors, as they address the primary tumors compared to metastases.

The response filed on 2/28/2007 further asserts that control blood was obtained from peripheral blood lymphocytes and LOH by comparison to those lymphocytes

resulted in a $p<0.05$ in patients. This argument has been considered but is not found persuasive because the specification does not teach the use of peripheral blood lymphocytes as a control for LOH comparisons.

The response filed on 2/28/2007 asserts on page 13, that newly amended claims 17 and 26 are fully enabled for staging and monitoring progression of melanoma and colon cancer. This argument has been fully considered but is not found persuasive because the specification teaches LOH frequencies in primary melanomas were 20%, 31%, 13% and 17% at D12S1657, D12S393, D12S1706, and D12S346, respectively (see table 1). The specification teaches LOH frequencies in metastatic melanomas were 23%, 35%, 17% and 21% at D12S1657, D12S393, D12S1706, and D12S346, respectively (see table 1). It thus appears that loss of the markers does not appear to differ greatly between primary and melanoma metastasis. The response does correctly identify the specification teaches there is significantly higher allelic imbalance in primary melanomas compared to metastatic melanomas ($p=0.02$), (see page 24, line 12), however the specification continues on page 25, to teach there was no significant differences between AJCC stage III and STAGE IV cancers (see page 25, lines 1-4), therefore the claims are not enabled for staging of melanoma, breast or colon cancer. The specification further teaches that further analysis resulted in division of type III tumors into ITM and RLM, but there was still no statistical relationship ($p=0.09$)(see Page 25, line 8). Thus there is no predictable relationship between the recited markers and staging or progression of melanoma.

Although the response asserts the claims with respect to colon cancer are enabled, the response directs the examiner to pages 18-31 and no teachings with respect to colon cancer were found. The response asserts the relevance of the markers to colon cancer are confirmed by applicants post-filing art publication of Umentani, et al (Oncogene (2004) volume 23- pages 8292-8300). The post-filing art further confirms that adenomas (a type of colon cancer) did not have allelic imbalance at the APAF-1 locus (see page 8295, 1st column, 1st full paragraph). Umentani et al further teaches that the allelic imbalance had no significant correlation with outcome. The teachings of Umenati do appear to teach that allelic imbalance of APAF-1 can be used to score the differences between primary and metastatic colon cancer, it does not teach that applicant possessed this information at the time the invention was filed or that the claims are enabled to stage between adenomas and metastasis.

The response of 2/28/2007 on page 14 further asserts that newly amended claim 35 and 58 are completely enabled by example 2 of the specification pages 31-40. This argument has been fully considered but has not been found persuasive because while the specification teaches the use of pre-biochemotherapy serum as the sample for determining LOH of the recited markers. The specification teaches responders to biochemotherapy have LOH at any of the recited markers, however the election is drawn to the LOH of all of the markers. The specification is thus not enabling for the elected invention.

The response of 2/28/2007 on page 14 further asserts that newly amended claim 44 fully enabled by the specification. The newly amended claim 44 is drawn to

determining the probability of survival of a human subject with stage III or IV melanoma by the LOH of D12S1657, D12S393, D12S1706, and D12S346 in "any" sample containing DNA. This is not found persuasive because the specification is not enabling for the detection of LOH in muscle cells as an indicator of survivability in melanoma. Further the specification further appears to teach that allelic imbalance is found in both patients that respond and do not respond after biochemotherapy (see page 36, lines 14-15). Thus patients that have responded to biochemotherapy would be considered to have a low chance of survivability based on the claims. It is unclear how a patient that has responded to treatment would be considered to have a low probability of survival.

Further the newly amended claim 93 that corresponds to initial claims 14 and 15 are not enabled for the reasons stated above, as well as the fact the specification does not teach a correlation exists between LOH of the recited markers and either breast or colon cancer.

4. Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejected claims 1, "any" markers of 12q22-23 region extending from D12S1657 to DS12S346 in a human subject. The claims set forth structural limitation that loss of markers to 12q22-23 region " markers of 12q22-23 region extending from D12S1657 to DS12S346 in a human subject be associated with cancer.

When the claims are analyzed in light of the specification, the invention encompasses an enormous number of nucleotide molecules and their combinations. The specification teaches markers: D12S1657, D12S393, D12S1706, and D12S346. The specification teaches loss of D12S1657, D12S393, D12S1706, and D12S346 is correlated with decreased APAF-1 expression. The specification does not teach any other marker in the recited region. The specification does not teach that the structure of 12q22-23 region is conserved across species.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been disclosed by complete structure. The instant specification teaches12q22-23 makers: D12S1657, D12S393, D12S1706, and D12S346. The species described in the specification is not representative of the genus of nucleotides encompassed by markers of 12q22-23 regions extending from D12S1657 to DS12S346 in a human subject.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g. other nucleotide sequences or positions with in a specific gene or nucleic acid), specific features and functional attributes that would distinguish different members of the claimed genus. While the claims and specification disclose an association of melanoma with the recited 12q22-23 markers such a functional limitation cannot be considered as a distinguishing feature because the structure of the described markers varies greatly. The skilled artisan would not be able to ascertain a structure/function relationship between recited markers and by markers of 12q22-23 region extending from D12S1657 to DS12S346 in

a human subject. The claims read in light of the specification encompass any nucleic acid molecule capable of being a marker of the 12q22-23 region extending from D12S1657 to DS12S346. This region encompasses millions of bases. Markers for 12q22-23 would thus encompass any combination of nucleotides that would hybridize to 12q22-23, from 10 nucleotides to the full length of the 12q22-23 region extending from D12S1657 to DS12S346. Thus "any" marker or combination of markers to the 12q22-23 region extending from D12S1657 to DS12S346 encompasses thousands of nucleotide sequences. The specification only teaches a statistical correlation of the recited markers with melanoma in humans.

In the instant application, the provided information regarding nucleic acid "any" marker of 12q22-23, does not constitute an adequate written description of the broad subject matter of the claims, and so one of skill in the art cannot envision the detailed chemical structure of the nucleic acids encompassed by the claimed 12q22-23 markers extending from D12S1657 to DS12S346. Adequate written description requires more than a statement that nucleic acids with a particular quality are part of the invention and reference to a potential method for their identification. The nucleic acid sequence is required.

In conclusion, the limited information provided regarding "any" 12q22-23 marker extending from D12S1657 to DS12S346 is not deemed sufficient to reasonably convey to one skilled in the art nucleic acid molecules encompassed.

Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded that the specification does not provide adequate written

description for the claims, except 12q22-23 markers: D12S1657, D12S393, D12S1706, and D12S346.

Response to arguments

The Response of 2/28/2007 on page 15, asserts that the amended claims have adequate written description. These arguments are not found persuasive for claims 1-3, and 5 although persuasive for 6-8, 10-19, 21-28, 30-37, 39-47, 49-61, 63-70, and 74-80. Newly amended claims 6-8, 10-19, 21-28, 30-37, 39-47, 49-61, 63-70, and 74-80 are drawn to detection of markers D12S1657, D12S393, D12S1706, and D12S346 for which the specification does have adequate written description. However, claims 1-3 and 5 are drawn to the detection of one or more markers extending from D12S1657 to D12S346. This as described previously and re-iterated above is an enormous number of nucleic acids that are not adequately supported by the instant specification. This rejection is maintained.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 74-80 and newly amended claims 6-10, 12-13, 17-19,21, 26-28, 30, 35-37, 29, 44-47, 49, 52-53, 58-61, 63, 82-96 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In response to the restriction response applicant elected all markers recited, and canceled all previous claims directed to possible combinations or subcombinations. Applicant added by amendment claims 74-80, which recite "any" combination of

markers recited. It is unclear if the combination is one, two, three, or four markers. The metes and bounds of the claims are unclear in view of the restriction response.

Newly amended claim 6-10, 12-13, 17-19,21, 26-28, 30, 35-37, 29, 44-47, 49, 52-53, 58-61, 63, 82-96 are drawn to the "DNA markers including." It is unclear if including is comprising, consisting or including a subset of markers. This rejection can easily overcome by amending the claim to recites "DNA markers comprising" or "DNA markers consisting."

Response to arguments

The response of 2/28/2007 asserts on page 15 that there is nothing ambiguous about the combination of the 4 markers. This argument has been fully considered but is not deemed persuasive because, in response to the restriction the combination of all four recited markers were elected, however claim 74 reads a combination of recited markers. "A combination" is broadly interpreted as "any" combination of the recited markers and thus not only encompasses the 4 recited markers, but any subcombination of markers as well and as such is indefinite. If the applicants intend to claim the combination amendment to the "combination of D12S1657, D12S393, D12S1706, and D12S346" could be recited.

Further the response amended claims 6-10, 12-13, 17-19,21, 26-28, 30, 35-37, 29, 44-47, 49, 52-53, 58-61, 63, 82-96 to recite "including" as described above.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Newly amended claims 17, 21, 22, 26, 30, 35, 39, 58, 59, 63, 64, 74 are rejected under 35 U.S.C. 102(b) as being anticipated by Soegnas, et al (Nature, 2001, volume 409, pages 207-211).

As noted in the MPEP 211.02, " a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone." Further, in *Pitney Bowes Inc. v. Hewlett-Packard Co.*, 182F.3d 1298, 1305, 51 USPQ2d 1161, 1166 (Fed Cir. 1999) the court held that if the body of the claim sets forth the complete invention, and the preamble is not necessary to give "life, meaning and vitality" to the claim, "then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation." In the present situation, steps of independent claims 1, 6, 17, 26, 35, and 58 are able to stand-alone and the preamble limitation is not accorded patentable weight. Accordingly, the claim language of the preamble to claims 1, 6, 17, 26, 35, and 58 merely sets forth the intended use or purpose of the claimed methods, but does not limit the scope of the claims.

As the specification does not specifically state a definition of acellular DNA, acellular DNA is given its broadest reasonable interpretation of any DNA not contained in a cell, including DNA isolated from a cell, tumor, etc.

With regards to claims 30, 63, Soegnas teaches the use of markers encompassing the APAF-1 locus (see page 207, 2nd column, lines 17-19).

With regards to claims 17, 21, and 22, Soegnas teaches there is a high rate of APAF-1 LOH in metastatic melanoma (see page 207, column 2, lines 17-19), but not in primary melanoma (see page 208, 1st column, line 1). Soegnas thus teaches LOH of APAF-1 in melanoma indicates a high probability of metastatic cancer.

With regards to claim 26, Soegnas teaches loss of APAF-1 is associated with disease progression (see page 208, lines 2-4).

With regards to claims 35,39, 40, Soegnas teaches there is correlation of APAF-1 levels and response to adriamycin in melanoma cells (see page 209, column 1, lines 8-10). Soegans teaches that APAF-1 levels are lower in melanoma's due to APAF-1 LOH. Soegnas thus teaches APAF-1 LOH results in poor efficacy of treatment in melanoma.

With regards to claim 58, Soegnas teaches assessment of APAF1 status improves therapeutic management for patients, as it is a required for apoptosis and thus a marker of chemosensitivity (see page 210, 2nd column, lines 20-26).

With regards to claim 59, Soegnas teaches LOH analysis from tumor samples (see page 210, 2nd column, analysis of APAF-1 locus).

With regards to claim 64, Soegnas teaches melanoma and metastatic melanoma (see abstract; page 207 2nd column, lines12-14).

With regards to claims 74, Soegnas teaches markers recited (see figure 1B).

Response to arguments

The response filed on 2/28/2007 asserts that the newly amended claims 1 and 6 are drawn to acelluar DNA that exists in a subject. This is found persuasive for claims 1 and 6. However, claims 17, 21, 22, 26, 30, 35, 39, 58, 59, 63, 64, 74 no longer require accellular DNA.

The response further asserts on page 16, with respect to claims 17 and 26 that Soegnas does not teach the association of the recited markers with the probability of progressing melanoma or colon cancer. However, as previously stated, Soegnas teaches there is a high rate of APAF-1 LOH in metastatic melanoma by detection of D12S1657, D12S393, D12S1706, and D12S346 (see figure 1b, page 207, column 2, lines 17-19), but not in primary melanoma (see page 208, 1st column, line 1). Thus Soegnas does teach the association of LOH of recited markers with progression of melanoma, as primary to metastatic. Further the claims are drawn either melanoma or colon cancer and thus teachings of Soegnas with respect to melanoma does anticipate the claims.

The response further asserts that Soegnas does not teach information on LOH in primary melanoma samples at the bottom of page 16, then apparently contradicts itself by stating on the top of page 17 that there is a difference in the expression of APAF-1 in primary melanoma relative to metastatic. The instant claims do not require the determination of LOH in primary tumors, so the arguments addressed to the fact that Soegnas does not teach them are moot, as not required by the claim. Further the response asserts that the APAF-1 locus in the Soegnas paper is incorrect. In response

to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., Soegnas does not teach LOH in primary melanoma, and APAF-1 locus is incorrectly cited by Soegnas) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). As Soegnas does teach the recited markers it does anticipate the claims and is thus maintained.

The response further filed 02/28/2007 further asserts on page 17, that Soegnas does not anticipate claims 35 and 58 because Soegnas teaches that cells negative for APAF-1 are resistant to a chemotherapeutic agent, ADR, but asserts this cannot be further interpolated to conditions in vivo. This argument has been fully considered but is not found persuasive because, the response does not present any teachings to the contrary or suggestions that the cell lines are not representative of the in vivo response. Further the claims do not require the biochemotherapy be administered in vivo and thus is anticipated by the resistance in cell lines.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5, 6-8, 10, 11, 12, 13, 17-19, 21, 22, 26-28, 30, 31, 35-37, 39, 40, 58, 59-61, 63, 64, 74-78 and 80-81 and newly amended claims 81-96 are rejected under 35 U.S.C. 103(a) as being unpatentable over Soegnas, et al (Nature, 2001, volume 409, pages 207-211) in view of Gocke et al (US Patent 6156504).

As noted in the MPEP 211.02, " a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone." Further, in *Pitney Bowes Inc. v. Hewlett-Packard Co.*, 182F.3d 1298, 1305, 51 USPQ2d 1161, 1166 (Fed Cir. 1999) the court held that if the body of the claim sets forth the complete invention, and the preamble is not necessary to give "life, meaning and vitality" to the claim, "then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation." In the present situation, steps of independent claims 1, 6, 17, 26, 35, and 58 are able to stand-alone and the preamble limitation is not accorded patentable weight. Accordingly, the claim language of the preamble to claims 1, 6, 17, 26, 35, and 58 merely sets forth the intended use or purpose of the claimed methods, but does not limit the scope of the claims.

Soegnas et al teaches detection of lose of heterozygosity of 12q22-23 region in 24 patients using 6 12q22-23 microsatelite markers (see figure 1 and legend). Soegnas further teaches genomic DNA for tumor and normal cells were amplified by PCR. This is being interpreted as isolating genomic DNA, thus making it acellular.

Soegnas teaches loss of APAF1 and microsatellite markers in the 12q22-23 regions in patients are detected in metastatic melanoma (see abstract; page 207 2nd column, lines12-14). Soegnas further teaches genomic DNA for tumor and normal cells were amplified by PCR. This is being interpreted as isolating genomic DNA, thus making it acellular. Soegnas teaches detecting cancer by LOH of markers to 12q2-23.

Soegnas teaches there is a high rate of APAF-1 LOH in metastatic melanoma (see page 207, column 2, lines 17-19), but not in primary melanoma (see page 208, 1st column, line 1). Soegnas thus teaches LOH of APAF-1 in melanoma indicates a high probability of metastatic cancer.

Soegnas teaches loss of APAF-1 is associated with disease progression (see page 208, lines 2-4).

Soegnas teaches there is correlation of APAF-1 levels and response to Adriamycin in melanoma cells (see page 209, column 1, lines 8-10). Soegnas teaches that APAF-1 levels are lower in melanomas with APAF-1 LOH. Soegnas thus teaches APAF-1 LOH results in poor efficacy of treatment in melanoma.

With regards to claim 58, Soegnas teaches assessment of APAF1 status improves therapeutic management for patients, as it is a required for apoptosis and thus a marker of chemosensitivity (see page 210, 2nd column, lines 20-26).

Soegnas does not teach the use of plasma (claims 3,8, 19, 28, 61), serum (2, 7, 18, 27, 60) , or blood (claims 81, 82, 84, 86, 90, 92, 96) as a sample.

However, Gocke et al teaches the use of serum (2, 7, 19, 27,37, 60) or plasma (claims 3,8, 18, 28, 36, 61) (see title, abstract). Gocke teaches peripheral blood (claims

81, 82, 84, 86, 90, 92, 96); plasma or serum is easily accessible and amenable for DNA amplification (see column 2, lines 54-55). Gocke further teaches detection colon cancer (claims 14, 32,68), breast cancer (claims 15,33, 69) or brain cancer (claims 16, 34, 70) by this method (see column 30, line 55-58). Gocke et al further teaches that many studies have used nucleic acid amplification to detect intracellular DNA extracted from circulating cells in blood 9see column 2, line 56-60). Gocke teaches use of plasma or serum allows rapid and timely extraction and sensitive detection of extracellular tumor associated or extracellular mutated oncogenic DNA (see column 3, lines 60-63).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve Soegnas method of detecting 12q22-23 mutations by use of peripheral blood, plasma, or serum as taught by Gocke, because Gocke teaches plasma or serum is easily accessible and amenable for DNA amplification. The ordinary artisan would be motivated to improve Soegnas method of detecting 12q22-23 mutations by use of plasma or serum as taught by Gocke, because Gocke teaches plasma or serum is easily accessible and amenable for DNA amplification. The ordinary artisan would further be motivated because, Gocke teaches use of plasma or serum allows rapid and timely extraction and sensitive detection of extracellular tumor associated or extracellular mutated oncogenic DNA. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the instant invention was made, it must be considered that said ordinary skilled artisan would have had reasonable expectation of success in practicing the claimed invention.

Response to Arguments

The response of 2/28/2007 correctly on page 18 asserts that Soegnas et al does not teach detection of breast or colon cancer. However, Goecke does teach the detection of colon, breast and brain cancer by detection of extracellular DNA in the plasma or serum.

The 2/28/2007 response further asserts on page 18, reiterates the arguments that the response previously described for Soegnas. These arguments have been addressed previously as directed to the 102 rejections and are not persuasive as previously denoted.

The response further asserts on page 19, that the combination of Soegnas and Gocke would not necessarily result have a reasonable expectation of success, because acellular DNA is quickly degraded. This is not found persuasive because Gocke teaches his detection of extracellular, tumor associated nucleic acids in the serum or plasma of the humans permits the detection of proliferative disorders including cancer (see abstract). Gocke teaches this method provides for the diction of extracelullar tumor-derived or tumor-associated nucleic acids in a plasma or serum fraction of blood (see column 4, lines 34-38).

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated

by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 6, 17, 26 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 7, 9, 11, 17, and 23 of copending Application No. 10/809956. Although the conflicting claims are not identical, they are not patentably distinct from each other because although not identical, they are co-extensive in scope.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim 1 of instant invention is drawn to detecting any markers of 12q22-23 from an accellular sample. Claim 1 and 17 of '956 are drawn to detecting markers from an accellular sample.

Claim 6 of instant application is drawn to detection of LOH. Claim 7 of '956 is drawn to detection of LOH.

Claim 17 of instant application is drawn to staging cancer by LOH detection. Claim 9 and 20 of '956 are drawn to staging cancer by LOH.

Claim 26 of instant application is drawn to prognosing cancer by LOH. Claim 11 and 23 are drawn to prognosing cancer by LOH.

Response to Arguments

The applicant asserts in the response of 2/28/2007, that instant claims are allowable other than for the double patenting rejections.applicant will submit appropriate terminal disclaimers. This rejection is maintained.

New Grounds of rejection necessitated by amendment.

Claim Objections

9. Claims 1-6 are objected to because of the following informalities: Claims 1-6 recited in the second line "anddetecting". This is believed to be a typographical error and should be amended to recite, "and detecting."

Appropriate correction is required.

New Matter

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10, 12, 13, 85, 87, 89, 91, and 95 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a

way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The newly amended claims 1-10, 12, 13, 85, 87, 89, 91, and 95 drawn to, "wherein the DNA exists as accellular DNA in the subject." The newly amended claims are drawn to acellular DNA in a subject, which is not supported in the specification and new matter. The specification teaches that, " A cellular DNA can be obtained from a sample of biological fluid by deproteinizing the sample and extracting DNA according to the procedures well known in the art"(see page 10, lines 20-22). As the response of 2/28/2007 does not specifically point to where this idea of DNA exists as a cellular DNA in a subject, the specification does not appear to support "wherein the DNA exists as accellular DNA in a subject."

Newly amended claims 1-5 are drawn to, "one or more markers in the 12q22-23 region extending from D12S1657 to D12S346 on the DNA." The claims are drawn to the detection of one or more markers associated with D12S1657 to D12S346 on the DNA, which is new matter. The specification teaches detection of the markers D12S1657, D12S393, D12S1706, D12S346 (see examples 1 and 2, pages 18-40 of specification). The MPEP states in 2163, "a subgenus is not necessarily described by a genus encompassing it and a species upon which it reads." Thus the range defined by from D12S1657 to D12S346 on the DNA is new matter. The response of 2/28/2007 does not specifically point to support for the idea of "one or more markers in the 12q22-23 region extending from D12S1657 to D12S346 on the DNA." Thus this appears to be new matter.

Summary

No claims are allowed.

Conclusions

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven C. Pohnert whose telephone number is 571-272-3803. The examiner can normally be reached on Monday-Friday 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Steven Pohnert

JEANINE A. GOLDBERG
PRIMARY EXAMINER
5/9/07